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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/848,439	05/08/97	LAVALLIE	

EXAMINER

HM21/1125

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ART UNIT	PAPER NUMBER
1643	15

DATE MAILED: 11/25/98

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 9/21/98

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), ~~or thirty days,~~ whichever is longer, from the mailing date of this communication. Failure to respond within the ~~period for~~ response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 1-17 + 18-26 is/are pending in the application.
Of the above, claim(s) 18-26 is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 1-17 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☑ Notice to Comply with Requirements for Patent Applications Containing Sequence
☑ Notice of Reference Cited, PTO-892
☑ Information Disclosure Statement(s), PTO-1449, Paper No(s). 6
☑ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

1. The Election September 21, 1998 (Paper No. 13) in response to the Office Action of July 20, 1998 (Paper No. 10) is acknowledged and has been entered. Claims 1-26 are pending in the application and Claims 18-26 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions. Claims 1-17 are currently under prosecution.

2. Applicant's continued traverse of the restriction requirement between Groups I (claims 1-10 and 14-17) and III (claims 11-13) is noted. Upon review and reconsideration and in view of applicant's arguments, the restriction requirement between Groups I and III is withdrawn and Group III has been rejoined to Groups I. and II. Further, Applicant's election with traverse of species (a) (species a of claim 1 and SEQ ID NO:2 of claim 2) in Paper No. 13 is acknowledged. However, upon review of the specification it was discovered that amino acids 1-275 of SEQ ID NO:3 (recited in claim 2) are identical to amino acids 21-295 of SEQ ID NO: 2 and thus it is clear that there is no undue search burden and the election of species requirement drawn to SEQ ID Nos 2 and 3 is withdrawn. This restriction requirement is final.

Specification

3. The specification on page 1 should be amended to reflect the status of the parent application serial number 08/796,153, now abandoned.

Sequences

4. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.8821 (a)(1) and (a)(2). However, this application fails to fully comply with the

requirements of 37 CFR 1.821 through 1.825 for the reasons(s) set forth on the attached Notice to Comply with Requirements for Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Specifically, the specification does not fully comply with the requirements of 37 CFR 1.821 through 1.825 because sequences disclosed in the specification, for example, on pages 15, 16, 40, 47 and 48 are not set forth in the Sequence Listing submitted with the application, nor are these disclosed sequences assigned separate identifiers. Examiner has made an effort to identify instances where nucleotide and/or amino acid sequences are disclosed but not identified or submitted on a Sequence Listing. Applicant must carefully review the specification to assign separate identifiers for all nucleotide sequences of ten or more nucleotides and/or amino acid sequences of four or more amino acids and to submit the disclosed sequences in a Sequence Listing in both paper and computer readable forms.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

6. Claims 1-6 are rejected under 35 USC 112, first paragraph because the specification, while being enabling for an isolated DNA sequence comprising the recited fragments of SEQ ID NO:1 and an isolated DNA sequence comprising a

DNA sequence which encodes the recited amino acid fragments of SEQ ID NO: 2 and SEQ ID NO:3 (claims 1 and 2) and vectors comprising said DNA sequences (claims 3 and 4) and host cells transformed with said vectors (claims 5 and 6), does not reasonably provide enablement for DNA sequences which hybridize to an isolated DNA sequence comprising the recited fragments of SEQ ID NO:1 or a DNA sequence which encodes the recited amino acid fragments of SEQ ID NO: 2 or SEQ ID NO:3, under stringent conditions and which encode a protein which exhibits Frazzled activity (claims 1 and 2), and vectors comprising said DNA sequences (claims 3 and 4) and host cells transformed with said vectors (claims 5 and 6). The specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to use or make the invention commensurate in scope with these claims.

The claims are drawn to DNA molecules which hybridize "under stringent conditions" to a DNA sequence comprising the recite fragments of SEQ ID NO: 1 and DNA encoding the recited fragments of SEQ ID NO: 2 and 3 and which encode a protein with "Frazzled protein activity". This includes all DNA molecules that hybridize under "stringent hybridization conditions", as disclosed in the specification, with the recited fragments of SEQ ID NO:1 or DNA sequences that encode the recited fragments of SEQ ID Nos 2 or 3. The specification provides one example of stringent conditions on page 12 lines 19-20 (the example is not limiting) and cites Maniatis, 1982 on page 8 lines 9-10 in connection with DNA sequences which hybridize under stringent conditions (again not limiting). Thus, stringent hybridization conditions as disclosed by the specification include the entire range of

stringent conditions from very low, or permissive to very high stringency conditions and the claimed hybridized sequences read on molecules that range from those that lack significant complementarity to those that are completely complementary to the claimed DNA. In addition, the specification teaches that the protein encoded by SEQ ID NO:1 may be used in regulating the binding of Wnt genes to their receptor, may be used for inducing formation, growth, differentiation, proliferation and/or maintenance of chondrocytes and/or cartilage tissue and for other tissue repair, such as pancreatic tissue repair (see abstract) and further teaches that frazzled protein activity refers to the ability to (I) bind Wnt proteins, (ii) regulate the binding of Wnt proteins to Frizzled receptors, (iii) regulate the formation, differentiation, proliferation and/or maintenance of cells and/or tissue (page 4, lines 22-29) but does not in any way limit these activities. It is noted that the term "regulate" is not defined so that any impact of the encoded protein on the above cellular processes is encompassed by the claims. One cannot extrapolate the teaching of the specification to the scope of the claims because the specification does not provide teachings or working examples which would provide sufficient guidance to allow one of skill in the art to identify which of the multitude of polynucleotide sequences encompassed by the scope of the claims exhibits a frazzled activity or which activity it exhibits or provide sufficient guidance to use the multitude of polynucleotide sequences encompassed by the scope of the claims. Clearly, the instant situation is clearly amenable to the type of analysis set forth in *Ex parte Maizel* (27 USPQ2d 1662 at 1665) where it was found that:

> "Appellants have not chosen to claim the DNA by what it is but, rather, by what it does, i.e., encoding either a protein exhibiting certain characteristics, *or* a biologically functional equivalent thereof. Appellants' claims might be analogized to a single means claim of the type disparaged by the Court of Customs and Patent Appeals in *In re Hyatt*, 708F.2d 712, 218 USPQ 195 (Fed. Cir. 1983). The problem with the phrase "biologically functional equivalent thereof" is that it covers any conceivable means, i.e., cell or DNA, which achieves the stated biological result while the specification discloses, at most, only a specific DNA segment known to the inventor. Clearly the disclosure is not commensurate in scope with the claims."

Applying the same logic to the instant claims it is clear that the hybridizing DNA is claimed not by what it is but rather by what it does, that is that it hybridizes "under stringent hybridization conditions" to the recited fragments of SEQ ID NO:1 or DNA sequences that encode the recited fragments of SEQ ID Nos 2 or 3 and that it encodes a protein which exhibits Frazzled activity. As Frazzled activity is defined by the specification, most known proteins can be said to have such activity and therefore the claim covers a multitude of conceivable means, i.e. DNA sequences which hybridize to the DNA sequences recited above and which encode proteins which exhibit certain characteristics, while the specification discloses only a specific DNA segment known to the inventor that encodes a frazzled protein, and two amino acid segments (SEQ ID NO. 2 and SEQ ID NO.3) encoded by said DNA segment, the SDF-5 protein, and claims all sequences which hybridize to the recited sequences of SEQ ID NO:1 and

DNA sequences that encode SEQ ID Nos 2 and 3, under stringent hybridization conditions" which encode proteins that exhibit frazzled activity. Clearly the disclosure is not commensurate in scope with the claims. Hybridization under low or permissive stringent conditions would be expected to result in the detection of DNA sequences which encode proteins which, while they exhibit neither a structural nor a functional relationship to proteins encoded by the recited fragments of SEQ ID NO:1 or DNA encoding SEQ ID Nos 2 and 3, do indeed exhibit Frazzled activity as broadly defined by the specification. While, the specification provides examples 2, 3, 6 and 7 which are general assay protocols for determining if a protein has several types of frazzled activity, for example, BMP-like bone forming activity, no other guidance is provided to allow the skilled artisan to predict or identify which of the hybridizing DNA molecules encode proteins that exhibit any of the plethora of frazzled activities encompassed by the scope of the claims or provide guidance on or exemplification of assays which would be appropriate to test for the multitude of activities encompassed by the claims. Clearly, the specification does not teach how to make the invention as broadly claimed because the specification does not provide guidance or exemplification on how to identify which of the broadly claimed molecules exhibit frazzled activity or which frazzled activity they exhibit. In addition, the specification does not teach how to use the invention as broadly claimed because without identifying which frazzled activity the hybridizing DNA molecule encoded proteins exhibit, it would not be possible to use the DNA molecule to encode a protein that functions as that which is disclosed. Further, the specification does not teach how to use the multitude of DNA molecules that encode proteins encompassed by the claims if they do not encode

proteins that can be used for regulating the binding of Wnt proteins to their receptor, inducing formation, growth, differentiation, proliferation and/or maintenance of chondrocytes and/or cartilage tissue or for other tissue repair, such as pancreatic tissue repair. In view of the above, one of skill in the art would be forced into undue experimentation in order to practice the invention as claimed.

7. Claims 15-16 are rejected under 35 USC 112, first paragraph because the specification, while being enabling for a method for producing purified human SDF-5 protein comprising culturing a host cell transformed with an isolated DNA sequence comprising the recited fragments of SEQ ID NO:1 and an isolated DNA sequence comprising a DNA sequence which encodes the recited amino acid fragments of SEQ ID NO: 2 and SEQ ID NO:3, recovering and purifying said SDF-5 protein from the culture medium, does not reasonably provide enablement for a method for producing purified human SDF-5 protein comprising culturing a host cell transformed with an isolated DNA sequence comprising a DNA sequence that hybridizes under "stringent hybridization conditions" to a DNA sequence comprising the recited fragments of SEQ ID NO:1 or a method for producing purified human SDF-5 protein comprising culturing a host cell transformed with an isolated DNA sequence comprising a DNA sequence that hybridizes under "stringent hybridization conditions" to an isolated DNA sequence comprising a DNA sequence which encodes the recited amino acid fragments of SEQ ID NO: 2 and SEQ ID NO:3, recovering and purifying said human SDF-5 protein from the culture medium. The specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to use or make the invention commensurate in scope with these claims.

The claims are drawn to a method of producing purified SDF-5 protein comprising expressing a host cell comprising a DNA sequence which hybridize under "stringent hybridization conditions" as disclosed above. This includes all DNA sequences that hybridize to the claimed DNA sequences across the entire range of stringent hybridization conditions. The specification identifies SEQ ID NO:1 as human SDF-5 DNA (page 3, line 25) and identifies SEQ ID Nos 2 and 3 as human SDF-5 protein and human SDF-5 mature protein, respectively (page 3 lines 26 and 27) but does not limit SDF-5 DNA or protein to the identified SEQ ID Nos. Clearly, since SDF-5 protein is produced by a DNA that hybridizes under stringent conditions to a DNA comprising the recited fragments of Seq ID NO: 1 which encode a protein that exhibits frazzled activity, as well as a DNA that hybridizes under stringent conditions to a DNA comprising nucleotides encoding the recited fragments of SEQ ID Nos 2 and 3 which encode a protein that exhibits frazzled activity, all of these broadly claimed molecules encode SDF-5 protein. The teaching of the specification drawn to "stringent hybridization conditions" and "frazzled protein activity" are disclosed above. One cannot extrapolate the teaching of the specification to the scope of the claims essentially for the reasons drawn to the rejection of claims 1 and 2 above, that is that the specification does not teach how to make the invention as broadly claimed because the specification does not provide guidance or exemplification on how to identify which of the broadly claimed DNA molecules encode proteins which exhibit frazzled activity or which frazzled activity they exhibit, therefore they can't be used to make a method to produce a purified SDF-5 protein. In addition, the specification does not teach how to use the invention as broadly claimed because without identifying which frazzled

activity the hybridizing DNA molecule encoded proteins exhibit, it would not be possible to use the instant method to produce a protein that functions as that which is disclosed. Further, one cannot extrapolate the teaching of the specification to the scope of the claims because it was well known in the art at the time the invention was made that, as taught in Watson et al (Molecular Biology of the Gene, 4th Edition, 1987, The Benjamin/Cummings Publishing Company, Inc, Menlo Park, p. 85) that during transcription, only one of the two strands of DNA (the coding strand) becomes translated into RNA and further teaches that the two strands are complementary but not identical and are expected to code for completely different polypeptides (p. 85). Thus, it would not be expected by one of ordinary skill in the art that a DNA sequence that hybridizes under stringent conditions, even if fully complementary to SEQ ID NO:1, would encode a human SDF-5 protein, thus the specification does not teach how to make a method of producing a SDF-5 protein using a hybridizing DNA molecule that is, by definition, complementary to the DNA encoding SDF-5 protein or how to use the method to produce a SDF-5 protein using the hybridizing DNA molecule as the starting material. In view of the above, one of skill in the art would be forced into undue experimentation in order to practice the invention as claimed.

8. Claims 7-9 are rejected under 35 USC 112, first paragraph because the specification, while being enabling for an isolated DNA sequence comprising the recited fragments of SEQ ID NO:1 and equivalent degenerative codon sequences thereof as well as a vector comprising said DNA molecules and a host cell transformed with said vector does not reasonably provide enablement for naturally occurring allelic variants of said DNA sequence, or vectors comprising said allelic variants or host cells

transformed with said vectors. The specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to use or make the invention commensurate in scope with these claims.

The claims are drawn to allelic variants of the recited fragment of SEQ ID NO:1. This includes all allelic variants, regardless of whether the variants result in changes in the peptide sequence. The specification teaches that "Allelic variations of the sequences of SEQ ID NO:1, whether such nucleotide changes result in changes in the peptide sequence or not..... are also included" (page 8, lines 14-18) and teaches that allelic variants "(naturally-occurring base changes in the species population which may or may not result in amino acid change)" of DNA sequences which code for human SDF-5 protein coded for by the sequence of SEQ ID NO:1 also encode the novel factors described herein (on page 12, lines 26-31), that is proteins with frazzled activity as broadly claimed. One cannot extrapolate the teaching of the specification to the scope of the claims essentially for the reasons disclosed above drawn to hybridizing sequences that do not encode proteins with either structural nor functional relationship to the protein encoded by the claimed DNA sequences because although the specification teaches that allelic variants are naturally-occurring base changes in the species population which may or may not result in amino acid changes and Reiger et al (Glossary of Genetics and Cytogenetics, Classical and Molecular, 4th Ed., Springer-Verlay, Berlin, 1976) clearly define alleles as one of two or more alternative forms of a gene occupying the same locus on a particular chromosome..... and differing from other alleles of that locus at one or more mutational sites (page 17), the specification provides neither guidance on nor exemplification of how similar the allelic variants

must be to SEQ ID NO:1 in order to encode and therefore produce proteins that function as disclosed, or how to identify those allelic variants that produce proteins that function as disclosed or how to use those allelic variants that produce proteins with frazzled activities that have not been identified. Clearly, it would be expected by one of ordinary skill in the art that a substantial number of allelic variants would encode proteins with neither structural nor functional relationship to the protein encoded by the claimed isolated DNA molecule comprising the recited fragment of SEQ ID NO:1. As disclosed above, it is clear that the specification does not teach how to make or use the invention as claimed and one of skill in the art would be forced into undue experimentation in order to practice the invention as claimed.

9. Claim 17 is rejected under 35 USC 112, first paragraph because the specification, while being enabling for a method for producing purified human SDF-5 protein comprising culturing a host cell transformed with an isolated DNA sequence comprising the recited fragments of SEQ ID NO:1 and equivalent codon sequences thereof, recovering and purifying said human SDF-5 protein from the culture medium does not reasonably provide enablement for a method for producing purified human SDF-5 protein comprising culturing a host cell transformed with an isolated DNA sequence comprising an allelic variant of the recited fragment of SEQ ID NO: 1, recovering and purifying said human SDF-5 protein from the culture medium. The specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to use or make the invention commensurate in scope with these claims.

The claims are drawn to a method of producing purified SDF-5 protein comprising expressing a host cell comprising culturing a host cell transformed with an allelic variant of the recited fragment of SEQ ID NO:1. This includes all allelic variants, regardless of whether the variants result in changes in the peptide sequence. The teaching of the specification is disclosed above. One cannot extrapolate the teaching of the specification to the scope of the claims essentially for the reasons drawn to the rejection of claims 1 and 2 above, that is that the specification does not teach how to make the invention as broadly claimed because the specification does not provide guidance or exemplification on how to identify which of the broadly claimed allelic variants encode proteins which exhibit frazzled activity or which frazzled activity they exhibit, therefore they can't be used to make a method to produce a purified SDF-5 protein. In addition, the specification does not teach how to use the invention as broadly claimed because without identifying which frazzled activity the allelic variant encoded proteins exhibit, it would not be possible to use the instant method to produce a protein that functions as that which is disclosed. Further, the specification does not teach how to use the multitude of allelic variants that encode proteins encompassed by the claims if they do not encode proteins that can be use for regulating the binding of Wnt proteins to their receptor, inducing formation, growth, differentiation, proliferation and/or maintenance of chondrocytes and/or cartilage tissues or for other tissue repair such as pancreatic tissue repair. For these reasons it is clear that the specification does not teach how to make or use the invention as claimed and one of skill in the art would be forced into undue experimentation in order to practice the invention as claimed.

10. Claims 7-9 and 17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case only sets forth SEQ ID NO:1 and equivalent degenerative codon sequences thereof and therefore the written description is not commensurate in scope with the claims drawn to naturally occurring allelic sequences of a DNA molecule comprising a DNA sequence consisting of nucleotides 316-1143 of SEQ ID NO:1.

It is noted that claims 7 and dependent claims 8, 9 and 17 have been interpreted to be drawn only to human SDF-5 molecules because SEQ ID NO:1 has been defined as encoding a human SDF-5 protein (p. 2, lines 28-30).

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

Reiger et al (Glossary of Genetics and Cytogenetics, Classical and Molecular, 4th Ed., Springer-Verlay, Berlin, 1976) clearly define alleles as one of two or more alternative forms of a gene occupying the same locus on a particular chromosome..... and differing from other alleles of that locus at one or more mutational sites (page 17).

Thus, the structure of naturally occurring allelic sequences are not defined. With the exception of SEQ ID NO:1, the skilled artisan cannot envision the detailed structure of the encompassed polynucleotides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016.

Furthermore, In *The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

Support for allelic variants is provided in the specification on page 8, lines 14-18 where it is disclosed that "Allelic or other variations of the sequences of SEQ ID NO:1, whether such nucleotide changes result in changes in the peptide sequence or not..... are also included" and on page 12, lines 26-31 where it is disclosed that allelic variants

of DNA sequences which code for human SDF-5 protein coded for by the sequences of SEQ ID NO:1 also encode the novel factors described herein. However, no disclosure, beyond the mere mention of allelic variants is made in the specification. This is insufficient to support the generic claims as provided by the Interim Written Description Guidelines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645.

Therefore only an isolated DNA molecule comprising a DNA sequence consisting of nucleotides 316-1143 of SEQ ID NO:1 and equivalent degenerative codon sequences thereof, but not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph.

11. Claims 1-6, 11-13 and 15-16 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(A) Claims 1-6 and 15-16 are indefinite because claims 1 and 2 recite the phrase "stringent hybridization conditions". Stringent conditions are not defined by the claim (which reads on the full range of stringent conditions, that is from very permissive to very high stringency), the specification does not provide a standard for ascertaining the requisite degree of stringent conditions and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention and would not be able to determine the metes and bounds of the claims.

(B) Claims 11-13 are indefinite because claim 11 recites the phrase "suitable signal peptide". The phrase is indefinite because it is not clear what the peptide is suitable for nor what features of the peptide are required in order to be suitable.

© Claims 15-16 are indefinite because claims 15-16 recite the phrase "method for producing purified human SDF-5 protein". The claims are confusing because it is not clear whether the SDF-5 protein is a discrete protein or a member of a family of proteins because as written, the claims are drawn to purification of human SDF-5 by culturing DNA sequences according to claims 1, 2 and 7 which include DNA sequences which hybridize under stringent conditions, as disclosed above, to SEQ ID NO:1 or an isolated DNA sequence which encodes SEQ ID NO:2 and which clearly would be expected to include nonhuman DNA sequences.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

13. Claims 1 and 2 are rejected under 35 USC 102(a) as being anticipated by Wang et al (JBC., 1996, 271:4468-4476, IDS Item, C2, see also Database Search, US-08-848-439-1.rge).

Because of the indefinite nature of the phrase "stringent hybridization conditions" it is assumed for examination purposes that those conditions read on permissive or low stringent hybridization conditions.

Because of the indefinite nature of the phrase "exhibits Frazzled activity" it is assumed for examination purposes that any impact of the encoded protein on the cellular processes of formation, differentiation, proliferation and/or maintenance of cells and/or tissues is encompassed by the claims.

Claims 1 and 2 are drawn to an isolated DNA sequence comprising a sequence which hybridizes to a DNA sequence comprising nucleotides 256-1140 of SEQ ID NO:1 and an isolated sequence comprising a sequence which hybridizes to a DNA sequence encoding amino acids 1-295 of SEQ ID NO: 2 (which reads specifically on nucleotides 256-1140 of SEQ ID NO:1 since the specification teaches that nucleotides 256-1140 of SEQ ID NO:1 encode amino acids 1-295 of SEQ ID NO:2) under stringent hybridization conditions and encode a protein which exhibits *Frazzled* activity.

Wang et al teach a DNA sequence (see p. 4468 italicized sentence at the bottom of the column and US-08-848-439-1.rge, result 3) with 49 nucleotides complementary to SEQ ID NO: 1 that would hybridize to nucleotides 418-690 of SEQ ID NO:1 under permissive stringent hybridization conditions and thus would hybridize to a fragment of SEQ ID NO:1 as disclosed. The protein encoded by the DNA is a Frizzled protein that is expected to be important for signal transduction and intracellular transmission of information (p. 448, col 1). Clearly, signal transduction was known to be important for the regulation of formation, differentiation, proliferation and/or maintenance of cells and/or tissue. The reference clearly suggests that the protein is believed to have this activity and inasmuch as the definition of frazzled activity recited in the specification

reads on the expected activity of the referenced encoded protein, said encoded protein meets the requirements of the claims.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

15. Claims 1-6 are rejected under 35 U.S.C. § 103 as being unpatentable over Wang et al as applied to claims 1 and 2 and further in view of in view of US Patent No.

4,889,806 and Sambrook et al (Molecular Cloning, A Laboratory Manual, , Cold Spring Harbor, 1989, pp p. 16.3-4.)

The claims are drawn to an isolated DNA sequence comprising a sequence which hybridizes to a DNA molecule comprising nucleotides 256-1140 of SEQ ID NO:1 and an isolated sequence comprising a sequence which hybridizes to a DNA sequence encoding amino acids 1-295 of SEQ ID NO: 2 (which reads specifically on nucleotides 256-1140 of SEQ ID NO:1 since the specification teaches that nucleotides 256-1140 of SEQ ID NO:1 encode amino acids 1-295 of SEQ ID NO:2) under stringent hybridization conditions and encode a protein which exhibits *Frazzled* activity and a vector comprising said DNA molecule and a host cell transfected with said vector.

Wang et al et al disclose as set forth above but do not disclose the DNA molecule in a vector that has been transformed into a host cell.

US Patent No. 4,889,806 teach that with the advent of recombinant DNA and molecular cloning technology it is now conventional to transfer genetic information into plasmids or vectors constructed in vitro and then transferred into host cells and clonally propagated (col 1, lines 18-24).

Sambrook et al teach that cloned genes are conventionally expressed using expression vectors and that expression of cloned proteins have been used to: (1) confirm the identity of a cloned gene by using immunological or functional assays to detect the encoded protein; (2) produce large amounts of proteins of biological interest that are normally available in only limited quantities from natural sources; (3) to study the biosynthesis and intracellular transport of proteins following their expression in

various cell types; and (4) to elucidate structure-function relationships by analyzing the properties of normal and mutant proteins (para bridging pages 16.3 and 16.4).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the DNA molecule of Wang et all with the methods of Sambrook et al and US Patent No. 4,889,806 because US Patent No. 4,889,806 specifically teaches that it is conventional to transfer genetic materials into plasmids or vectors and then transfer the plasmids or vectors into host cells and clonally propagate the genetic material to produce the encoded protein and because Sambrook et al teach that cloned genes are conventionally expressed using expression vectors. One of ordinary skill in the art at the time the invention was made would have been motivated to combine the DNA of Wang et al with the methods of Sambrook et al and US Patent No. 4,889,806 because Sambrook et al specifically teach that expressed cloned proteins are used to: (1) confirm the identity of a cloned gene by using immunological or functional assays to detect the encoded protein; (2) produce large amounts of proteins of biological interest that are normally available in only limited quantities from natural sources; (3) to study the biosynthesis and intracellular transport of proteins following their expression in various cell types; and (4) to elucidate structure-function relationships by analyzing the properties of normal and mutant proteins.

16. Claims 10 and 14 are allowed because they are free of the art.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703)

305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached at (703) 308-4310. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar

November 23, 1998

Application No. 08/848,439

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 CFR 1.821 - 1.825 for the following reason(s):

See Attached Office Action, Paper # 15, page 3, Section 4

☑ 1. This application clearly fails to comply with the requirements of 37 CFR 1.821 - 1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.

☑ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 CFR 1.821(c).

☑ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 CFR 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 CFR 1.822 and/or 1.823, as indicated on the attached copy of the marked-up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A substitute computer readable form must be submitted as required by 37 CFR 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 CFR 1.821(e).

☐ 7.

Other: _____

Applicant must provide:

☑ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing"

☑ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification

☑ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 CFR 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d)

For questions regarding compliance with these requirements, please contact:

For Rules Interpretation, call (703) 308-1123
For CRF submission help, call (703) 308-4212
For PatentIn software help, call (703) 557-0400

Please return a copy of this notice with your response.